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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,426	07/06/2006	Mohamed Abdulkader Ibrahim	EX04-019C-US	6671

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MCDONNELL BOEHNEN HULBERT @ BERGHOFF LLP
300 SOUTH WACKER DRIVE
SUITE 3100
CHICAGO, IL 60606

EXAMINER	
MCDOWELL, BRIAN E	

ART UNIT	PAPER NUMBER
4161	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,426	IBRAHIM ET AL.	
	Examiner	Art Unit	
	BRIAN MCDOWELL	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/2/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *10-29 and 33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 30-31* is/are rejected.

7)☒ Claim(s) *32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/23/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

BEM

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 7/2/2008 is acknowledged. Applicant's elected specie is also acknowledged. This specie reads on claims 1-9, 30-32. Claims 10-29, 33-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely **traversed** the restriction (election) requirement in the reply filed on 7/2/2008. The traversal is on the ground(s) that the claims as a whole possess unity of invention. This is not found persuasive because it was found that the inventions listed as Groups I-VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: *The prior art (US 3,340,260 see col. 18, example 7) teaches a specie that read on claim 1. Therefore, the compounds and method are not novel and the invention lacks a special technical feature.*

In summary, the inventions do not possess a special technical feature because of the prior art stated above and thus, are subject to restriction. Applicant's reference to Markush and linking claim practice is not relevant, since the special technical feature of the invention had been broken.

The requirement is still deemed proper and is therefore made **FINAL**.

This application contains nonelected subject material within claims drawn to an

invention elected with traverse in the paper of 7/2/2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

An action on the merits of claims 1-9, 30-31 is contained herein.

Claim Objections

Claim 32 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can not depend on another multiple dependent claim. See MPEP § 608.01(n). Accordingly, claim 32 has not been further treated on the merits.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, as being indefinite in that it fails to point out what is included or excluded by the claim language.

In the instance of claim 30, applicant is claiming a compound (see #16, a carbon is attached to the pyrimidine ring instead of a nitrogen) that does not fall under the genus formula I in claim 1. There is insufficient antecedent basis for this limitation in the claim.

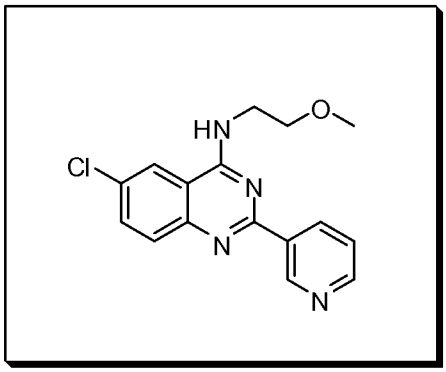
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated over Lee *et al.* (US Patent 5,436,233-cited by applicant in IDS).

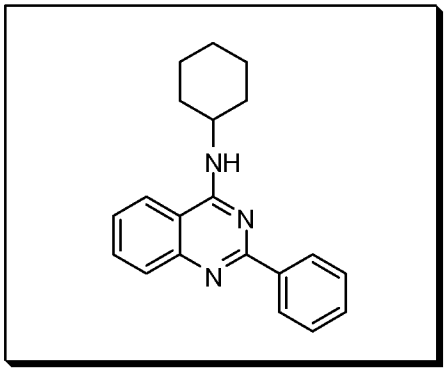
Lee *et al.* teaches the following compound:



Wherein X =OMe, one of Y = N, remaining Y = CH, $R^1 = R^2 = R^3 = R^5 = H$, and $R^4 = Cl$, (see page 72, example 12) that read on the aforementioned claim and is therefore anticipated.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated over Lee *et al.* (J.Med.Chem).

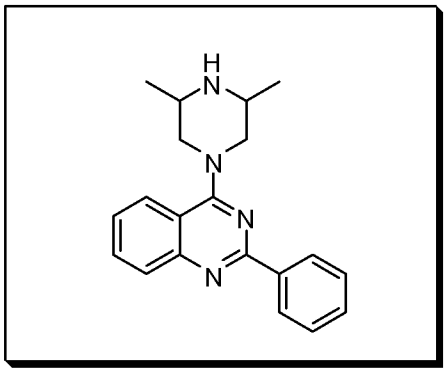
Lee *et al.* teaches the following compound:



Wherein Y = CH, X = R^3 = R^4 = R^5 = H, and R^1 and R^2 form a ring, (see page 3550, compound 26 in table 1) that read on the aforementioned claim and is therefore anticipated.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated over Chen *et al.* (US Patent 4,306,065).

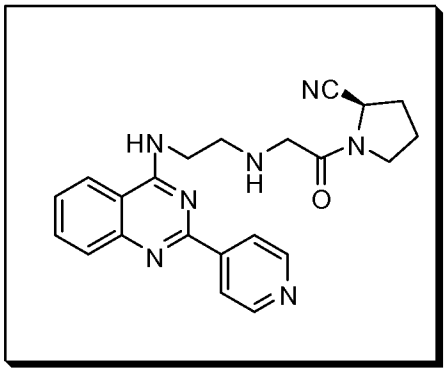
Chen *et al.* teaches the following compound:



Wherein Y = CH, $R^4 = R^5 = H$, and R^3 and R^2 form a ring, (see page 4, line 41, right column) that read on the aforementioned claim and is therefore anticipated.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated over Matsuno *et al.* (WO 02/051836).

Matsuno *et al.* teaches the following compound:



Wherein four of Y = CH, one of Y = N, $R^{1-5} = H$, and X = N(H)(lower substituted alkyl), (see page 21, compound 106) that read on the aforementioned claims and are therefore anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

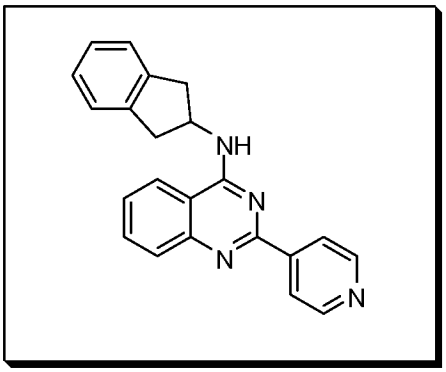
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.* (US Patent 5,436,233-cited by applicant in IDS) in view of Gibson *et al.* (Bioorg. and Med. Chem. Letters).

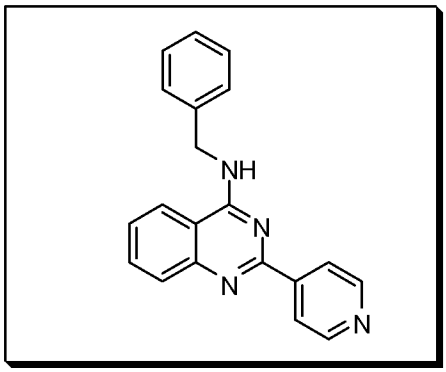
Claims 1-9, 30-31 refer to quinazolines and simple compositions of the general formula I.

Applicant's elected specie is the following compound below:



wherein X = R^1 = R^3 = R^4 = R^5 = H, as seen by the formula V in claim 13.

Lee *et al.* teaches the compound below (see page 37, example 3(q)):



The only difference between applicant's compound and the compound described by Lee *et al.* is the presence or lack of a five-membered carbocycle that is fused to the aryl ring. However, Gibson *et al.* has extensively studied varying the aniline moiety at the 4-position of quinazolines that serve as kinase inhibitors. In particular, it was shown that when placed at the 4-position of the quinazoline ring, the benzylamine moiety (compound taught by Lee *et al.*) and the indanyl moiety (instant application) possessed comparable biological activities (see page 2725, table 2, compounds 10 and 14, respectively). Thus the two moieties are interchangeable.

In summary, applicant is merely making an analogue of a known compound based on the teachings by Lee *et al.* and Gibson *et al.* It would be *prima facie* obvious to take the compound by Lee *et al.* and replace the benzylamine moiety with the indanyl amine system to achieve a predictable result (i.e., a biologically active compound that was derived from a well-known modification described by Gibson *et al.*). Therefore, the compound and said compound's compositions are obvious over the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, it does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a

prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is not found in the specification. c) There is no working example of a prodrug of a compound the formula I. d) The nature of the invention are quinazolines e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) One would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is

generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by claim 1.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular compound of unknown structure is, in fact, a prodrug.

Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compounds. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" hardly constitute instructions to the BS process chemist of how to make such a compound.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN MCDOWELL whose telephone number is

(571)270-5755. The examiner can normally be reached on Monday-Thursday 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BM

/Patrick J. Nolan/

Supervisory Patent Examiner, Art Unit 4161